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CIGARETTE SMOKING AND SCHIZOPHRENIA

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You asked for information on the therapeutic effects of cigarette smoking on individuals with schizophrenia.

The information in this report was obtained from a search of the PubMed and Cochrane Review databases. Clinical trials, meta-analyses, and systematic reviews completed since 2000 were considered for inclusion based on relevance; this search is not comprehensive and does not represent a complete review of the existing biomedical literature.

SUMMARY

Schizophrenia is a chronic, severe brain disorder that prevents a person from interpreting reality normally. It is characterized by a combination of hallucinations, delusions, and abnormal thinking and behavior. Individuals with schizophrenia have higher rates of smoking than both the general population and those with other mental illnesses, with studies estimating rates among this population ranging from 60-90% (Hahn, 2012). Moreover, individuals with schizophrenia are more likely to be heavier smokers, smoke stronger cigarettes, start smoking at a younger age, and extract more nicotine from their cigarettes than healthy smokers or those with other mental illnesses (Kelly, 2000). They are also much less likely to quit smoking and more likely to experience smoking-related morbidity and mortality. For example, smokers with schizophrenia are twice as likely to get cardiovascular disease and have a 20% shorter life expectancy than the general population (Winterer, 2010).

The reasons for higher smoking rates among individuals with schizophrenia are still unclear. Many within and outside the psychiatric community believe these individuals smoke as a form of self-medication because nicotine increases dopamine levels in the brain, which in turn reduces the side effects of anti-psychotic medications (such as tremors or depression), negative symptoms, and cognitive deficits related to their illness. Research regarding the effect of smoking on schizophrenic symptoms is inconclusive. While several studies show nicotine helps reduce negative symptoms and improve cognitive deficits, others have found little or no effect.

Researchers acknowledge methodological limitations in these studies. Many had very small sample sizes, lacked information on confounders, and, in some cases, were cross-sectional in design, thus only capturing data at a single point in time.

SCHIZOPHRENIA AND CIGARETTE SMOKING

Schizophrenia is a chronic, psychotic brain disorder characterized by a variety of symptoms. In addition to hallucinations and delusions (also called “positive symptoms”), individuals with schizophrenia experience (1) negative symptoms such as social withdrawal, dysfunctional relationships, avolition (lack of motivation or initiative), and flattened affect and (2) cognitive deficits including poor attention and memory impairments (Mobascher, 2008).

Cigarette smoking rates of individuals with schizophrenia are significantly higher than the general population and those with other mental illnesses. The reason for these higher rates is unclear, although many studies suggest these individuals smoke to self-medicate negative symptoms, cognitive deficits, and side effects of anti-psychotic medication.

Pharmacological Effects of Nicotine

The pharmacological effects of nicotine are complex and involve several systems in the body, although studies primarily focus on the central nervous system. Once it is inhaled, nicotine causes the up-regulation (i.e., increased availability) of nicotinic acetylcholine receptors throughout the brain. Nicotine binds to these receptors, resulting in the release of certain neurotransmitters, including dopamine and serotonin.

With respect to schizophrenia, raising dopamine levels in the brain may help alleviate negative symptoms by stimulating (1) certain processes involved with learning and cognition and (2) motor functions such as improved attention, active coping, and emotional engagement and response (Kumari, 2005). A recent study bears this out. It found a negative association between the availability of nicotinic acetylcholine receptors in the brain and negative symptoms in individuals with schizophrenia. The authors suggest that this could explain the high smoking rates among this population (D'Souza, 2012).

Effect on Anti-psychotic Medication Side Effects

Schizophrenia is primarily treated with psychiatric therapy and anti-psychotic medication. Research suggests that one reason individuals with schizophrenia smoke is to alleviate the side effects of these medications, which may include depression, blurred vision, restlessness, tremors, and muscle spasms. Specifically, anti-psychotic drugs block dopamine receptors in the brain and smoking overcomes this blockage by stimulating dopamine release (Winterer, 2010).

However, some studies suggest that the relationship between anti-psychotic medication and smoking depends on the type of medication used. Individuals taking “typical” antipsychotic medications (e.g., haloperidol, chlorpromazine, and thioridazine) smoke a significantly higher number of cigarettes than those taking “atypical” medications (e.g., clozapine, risperidone, and olansapine). This may be due to the different effect each type of medication has on the brain’s dopamine receptor system (Barnes, 2006). Atypical anti-psychotic medications have been shown to decrease negative symptoms by increasing dopamine levels in the brain in a similar way to nicotine. Those who switch from typical to atypical anti-psychotic medications often reduce their smoking levels. But, researchers have also found that smokers are more likely to gain therapeutic benefits from clozapine than non-smokers (Kumari, 2005).

While cigarette smoking has been shown to alleviate the side effects of anti-psychotic medication, it also increases the metabolism of these medications by up to 50%. This means that smokers with schizophrenia require higher medication dosages than non-smokers to achieve the same therapeutic effects (Sagud, 2009). Some researchers suggest that this under-medication partly explains why smokers with schizophrenia have higher hospitalization rates and more hallucinations and delusions during acute episodes than non-smokers (Winterer, 2010).

Effect on Cognitive Deficits

Individuals with schizophrenia experience several cognitive deficits, including learning, sensory gating (filtering out redundant or unnecessary stimuli from the brain, also called P50 deficits), and memory impairments; attention deficits; and reduced cognitive processing speed (Kumari, 2005). Research regarding the effect of cigarette smoking on cognitive deficits is mixed. While several studies have found that nicotine consumption improves cognitive deficits, (Krishnadas, 2012 and Winterer, 2010) others have found little or no association between smoking and cognitive deficits in schizophrenia (Barnes, 2006). A 2004 study by Harris found nicotine's effects were mostly limited to attention deficits.

Memory. Individuals with schizophrenia have deficits in different types of memory processing, which some researchers have found to be ameliorated by nicotine consumption. For example, a 2010 study by Dulude found that acute nicotine treatments normalized sensory memory processing in individuals with schizophrenia. Similar results were found in a 2008 study by Jubelt, which examined the effect of a single dose of nicotine on the episodic memory of non-smokers with schizophrenia. Those receiving the treatment recalled new information more accurately and rapidly than the non-smoking controls. Conversely, a 2002 study by Smith found the administration of nicotine nasal spray to smokers with schizophrenia after a period of smoking abstinence only modestly improved certain measures of verbal memory.

Attention Deficits. Poor attention is one of the primary cognitive deficits experienced by individuals with schizophrenia, regardless of disease severity or type of treatment (Hahn, 2012). Some studies have found that even a single dose of nicotine improves sustained attention in individuals with schizophrenia (Hong, 2011). A recent study suggests that nicotine improves selective attention in smokers with schizophrenia by acting as a “stimulus barrier” that filters out irrelevant and distracting stimuli from the individual's awareness, allowing him or her to focus on the task at hand (Fisher, 2012).

A 2011 study by Wing compared cognitive performance of individuals with schizophrenia based on their smoking status (i.e., smoker, non-smoker, or never smoked) and found that cognitive deficits, particularly those involving sustained attention, were most pronounced in non-smokers, especially those who had never smoked. An earlier study found

that exposing non-smokers with schizophrenia to a single dose of nicotine improved their performance on continuous performance tasks, a common measure of attention deficits (Barr, 2008).

Researchers have found similar results when administering nicotine to smokers with schizophrenia after a period of abstinence. One study found that administering a nicotine patch to smokers with schizophrenia after a period of nicotine withdrawal improved their performance on selective attention tasks. In contrast, healthy controls (i.e., smokers without mental illness) performed worse after receiving the nicotine patch (Jacobsen, 2004).

Conversely, some studies have found smoking has little or no effect on attention deficits in individuals with schizophrenia. For example, a 2011 study by Segarra found that while patients with first-episode schizophrenia who smoked performed better in attention measures than non-smoking patients, this superior performance was lost 12 months after taking anti-psychotic medications. The authors suggest that smoking may improve cognitive function in a similar manner as atypical antipsychotic medications and that these individuals start smoking in an effort to improve their symptoms before beginning their drug treatment.

In addition, a 2011 study by Hong suggests that there may be an overreliance on the self-medication theory as an explanation for increased smoking rates among individuals with schizophrenia. The authors found that administering a nicotine patch improved, but did not normalize, attention deficits in individuals with schizophrenia. Because the nicotine patch did not correct underlying brain abnormalities, and both the healthy comparison subjects and those with schizophrenia experienced improvements in attention, the authors propose that the nicotine effect is not disease specific and cannot entirely explain increased smoking rates among this population.

Other Sensory Processing Deficits. According to a 2010 review by Winterer, nicotine's stimulation of the brain's dopamine receptor system normalizes a number of sensory processing deficits associated with schizophrenia, including sensory, prepulse-inhibition (PPI, a decreased response to a startling stimulus), and eye-tracking deficits.

Study Limitations

In general, research regarding the therapeutic effects of smoking on individuals with schizophrenia has produced mixed results, which may be primarily due to study design. Many studies had very small sample

sizes, lacked information on confounders, and, in some cases, were cross-sectional rather than longitudinal, thus only capturing data at a single point in time.

For example, a 2012 study by Zhang found Chinese men with schizophrenia were heavier, more frequent smokers and less likely to quit than control subjects. Smokers also had significantly fewer negative symptoms than non-smokers with schizophrenia, supporting the self-medication theory. However, the study sample consisted of institutionalized men who had more severe forms of the disorder and had been treated with antipsychotic medications for almost 20 years, which may have affected the results. Also, because of its cross-sectional design, the authors were unable to establish causality between smoking and symptom severity.

In addition, studies have not adequately compared the different effects, if any, of acute versus chronic smoking on schizophrenia symptoms.

BIBLIOGRAPHY

Barnes M, Lawford BR, et al. Smoking and schizophrenia: is symptom profile related to smoking and which antipsychotic medication is of benefit in reducing cigarette use? *Austn Z J Psychiatry* 2006 Jun-Jul; 40(6-7):575-580.

Barr RS, Culhane MA, et al. The effects of transdermal nicotine on cognition in nonsmokers with schizophrenia and nonpsychiatric controls. *Neuropsychopharmacology* 2008 Feb;33(3):480-90.

D'Souza DC, Esterlis I, et al. Lower $\beta 2^*$ -nicotinic acetylcholine receptor availability in smoking with schizophrenia. *Am j Psychiatry* 2012 Mar; 169(3):326-34.

Dulude L, Labelle A, et al. Acute nicotine alteration of sensory memory impairment in smokers with schizophrenia. *J Clin Psychopharmacol* 2010; 30(5):541-548.

Fisher DJ, Grant B, et al. Nicotine and the hallucinating brain: effects on mismatch negativity (MMN) in schizophrenia. *Psychiatr Res* 2012 Apr 30; 196(2-3):181-187.

Hahn C, Hahn E, et al. Effects of smoking history on selective attention in schizophrenia. *Neuropharmacology* 2012 Mar; 62(4):1897-1902.

- Harris JG, Kongs S, et al. Effects of nicotine on cognitive deficits in schizophrenia. *Neuropsychopharmacology* 2004; 29:1378-1385.
- Hong LE, Schroder M, et al. Nicotine enhances but does not normalize visual sustained attention and the associated brain network in schizophrenia. *Schizophr Bull* 2011 Mar; 37(2):416-425.
- Jacobsen LK, D'Souza DC, et al. Nicotine effects on brain function and functional connectivity in schizophrenia. *Biol Psychiatry* 2004 Apr 15; 55(8):850-858.
- Jubelt LE, Barr RS, et al. Effects of transdermal nicotine on episodic memory in non-smokers with and without schizophrenia. *Psychopharmacology (Berl)* 2008 Jul;199(1):89-98.
- Kelly C and McCreadie R. Cigarette smoking and schizophrenia. *APT* 2000; 6:327-331.
- Krishnadas R, Jauhar S, et al. Nicotine dependence and illness severity in schizophrenia. *Br J Psychiatry* 2012 Aug 9; Epub ahead of print.
- Kumari V and Postma P. Nicotine use in schizophrenia: the self medication hypothesis. *Neurosci Biobehav Rev* 2005; 29(6):1021-1034.
- Mobascher A and Winterer G. The molecular and cellular neurobiology of nicotine abuse in schizophrenia. *Pharmacopsychiatry* 2008 Sep; 41 Suppl 1:S51-59.
- Sagud M, Mihaljevic-Peles A, et al. Smoking and schizophrenia. *Psychiatr Danub* 2009 Sep; 21(3):371-375.
- Segarra R, Zabala A, et al. Cognitive performance and smoking in first-episode psychosis: the self-medication hypothesis. *Eur Arch Psychiatry Clin Neurosci* 2011 Jun;261(4):241-50.
- Smith RC, Singh A, et al. Effects of cigarette smoking and nicotine nasal spray on psychiatric symptoms and cognition in schizophrenia. *Neuropsychopharmacology* 2002 Sep;27(3):479-97.
- Wing VC, Bacher I, et al. Neuropsychological performance in patients with schizophrenia and controls as a function of cigarette smoking status. *Psychiatr Res* 2011 Aug 15; 188(3):320-326.

Winterer G. Why do patients with schizophrenia smoke? *Curr Opin Psychiatry* 2010; 23:112-119.

Zhang XY, Liang J, et al. Cigarette smoking in male patients with chronic schizophrenia in a Chinese population: prevalence and relationship to clinical phenotypes. *PLoS One* 2012; 7(2):e30937.

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